Specification Amendments

Amendments to the Specification have been made to correct informalities. No new matter has been added.

Priority

The Examiner states that the claimed priority is valid "except for the claims drawn to neurodegenerative disease." It is believed that the amendment to the claims avoids the issue.

Obviousness-Type Double Patenting

Claims 106, 107 and 109-124 were provisionally rejected under 35 U.S.C., § 101 as claiming methods that are not patentably distinct over Claims 91-97 of co-pending application Serial No. 08/192,102. Applicants note that Application Serial No. 08/192,102 was issued August 12, 1997 as U.S. Patent No. 5,656,272. Claims 106, 107 and 109 have been cancelled. Applicants will file a terminal disclaimer upon resolution of the remaining rejections.

Rejection of Claims 123 and 124 Under 35 U.S.C. § 112, First Paragraph

Claims 123 and 124 are rejected under 35 U.S.C. § 112, first paragraph on the grounds that the specification while being enabling for some immune and inflammatory diseases, does not reasonably provide enablement for neurodegenerative diseases, malignant pathologies and alcohol-induced hepatitis.

Claim 123 has been amended to delete neurodegenerative diseases, malignant pathologies and alcohol-induced hepatitis, thereby avoiding the issue. Withdrawal of the rejection of Claims 123 and 124 is respectfully requested.

Rejection of Claim 112 Under 35 U.S.C § 112, Second Paragraph

Claim 112 is rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

The Examiner believes that the antibody cA2 should be referred to by its ATCC accession number, not by its laboratory name. Applicants disagree.

As discussed in previous responses in this case, the cA2 antibody has not been deposited with the ATCC, and therefore, it has no ATCC accession number. As stated in the Manual of Patent Examining Procedure, § 2172.01, "[a] fundamental principle contained in 35 U.S.C. § 112, Second Paragraph, is that Applicants are their own lexicographer." In addition, "a claim may not be rejected solely because of the type of language used to define the subject matter for which the patent protection is sought" § 2173.01. Applicants, in acting as their own lexicographers, created the designation cA2 for the specific chimeric anti-TNFα antibody disclosed in the application. The specification discloses the DNA and amino acid sequences of the heavy and light chain variable regions of the cA2 monoclonal antibody in Figure 16B, thereby defining the antibody and enabling a person of ordinary skill in the art to produce cA2 and screen antibodies which have the same or similar properties without undue experimentation.

Furthermore, in two related applications, Serial No. 08/013,413, now issued U.S. Patent No. 5,656,272, and Serial No. 08/324,799, which was recently allowed, claims drawn to cA2 were granted by the Examiner. Moreover, in the previous Office Action, the Examiner withdrew objections and rejections relating to the depositing of cA2. Accordingly, withdrawal of the rejection of Claim 112 is respectfully requested.

Rejection of Claims 106, 107, 109-111, 113-118 and 123 Under 35 U.S.C. § 103

Claims 106, 107, 109-111, 113-118 and 123 are rejected under 35 U.S.C. § 103 as being unpatentable over Shalaby *et al.* (*Transplantation*, 1989) or Brennan *et al.* (*The Lancet*, 1989) or Piguet *et al.* (*J. Exp. Med.*, 1987) or Piguet *et al.* (*J. Exp. Med.*, 1989) or Grau *et al.* (*Science* 1987) in the view of Möller *et al.* (U.S. Patent No. 5,231,024 or Cytokine, 1990) or Rathjen *et al.* (WO 91/02078) and Morrison *et al.* (*Science*, 1985, *225*:1202-1207) or Morrison *et al.* (Hospital Practice 1989).

Obviousness as a question of law is based on Graham v. John Deere Co., 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966). The text of the citation was provided in the previous response in this case. In appreciation of the Examiner's time, recitation has been omitted in this response.

The scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art all indicate that Applicants' invention is not obvious.

Applicants' invention is drawn to methods of treating TNFα-mediated disease in a human comprising administering TNF-inhibiting amounts of an anti-TNF chimeric antibody. Preferred claimed methods are directed to administering chimeric antibodies which competitively inhibit binding of TNF to cA2; antibodies which bind to epitopes between 87-108 or both 59-80 and 87-108 of a specified amino acid sequence of hTNF; antibodies which do not bind to specified epitopes of hTNF; and antibodies comprising variable regions comprising specific amino acid sequences or comprising polypeptides encoded by specific nucleotide sequences. Also claimed are methods drawn to the use of anti-TNF chimeric antibodies comprising an IgG1 constant region.

The Shalaby, Brennan, Morrison, Möller and Rathjen references were discussed at length in the response to the prior Office Action. It is noted with appreciation that, subsequent to

the previous Office Action, related case, Application Serial No. 08/324,799, which contains claims similar to those in the present application (drawn to methods of treatment for rheumatoid arthritis), was allowed by the Examiner. The claims in the 08/324,799 application were allowed over essentially the same references and their combinations. In addition, application Serial No. 08/192,102, now U.S. Patent No. 5,656,272, which also contains claims similar to those in this application (drawn to methods of treatment of Crohn's disease), was also allowed by the Examiner.

Applicants respectfully assert that the teachings of the references cited by the Examiner, either independently or in combination, do not support the conclusion that the claimed chimeric antibodies are to be used in an expected and obvious manner.

Teachings of Cited References

Shalaby, Brennan, Morrison, Möller and Rathjen

These references were discussed at length in the response filed on March 10, 1997 (pages 15-17), which is incorporated herein by reference.

Piguet *et al.* and Grau *et al.*

The teachings of Piguet *et al.* (1987 and 1989) and Grau *et al.* (1987), which are newly cited in this Office Action, are discussed in detail below.

1. Piguet *et al.*, 1987 and 1989

The Examiner states that Piguet *et al.* 1987 teach a method of preventing/treating GVHD in mice using anti-TNFα antibodies that almost entirely prevented the cutaneous and intestinal lesions of the acute-phase of GVHD and markedly reduced overall mortality.

The Examiner states that Piguet *et al.* 1989 teach a method of treating bleomycin-induced pneumopathy and fibrosis in mice, using anti-TNFα antibodies, that prevents alveolar damage, growth of fibroblasts, and collagen deposition.

Piguet *et al.* (1987 and 1989) describe the passive immunization of mice with IgG enriched fractions of a rabbit polyclonal antisera to TNFα. Following anti-TNFα treatment, significant decreases in indices of skin and intestinal lesions associated with acute phase GVHD (Piguet *et al.*, 1987) and bleomycin-induced pneumopathy and fibrosis (Piguet *et al.*, 1989) were reported. Piguet's observations utilizing rabbit polyclonal antibodies do not presuppose an expected use of monoclonal chimeric anti-TNFα antibodies in TNF-α-mediated disease as directed by the Applicant's invention.

Furthermore, the polyclonal antibodies described in the teachings of Piguet (1987 and 1989), as well as Brennan (1989) and Grau (1987), are genuinely distinct from the preferred antibodies in the Applicants' invention. Polyclonal antibodies do not possess the structural and functional specificity of monoclonal antibodies. Hence, the teachings of these references are even less relevant to the claims put forth in this case.

2. Grau *et al.* (1987)

The Examiner states that Grau et al. teach a method of preventing/treating cerebral malaria disease using anti-TNFα antibodies.

Following a single intravenous injection of a polyclonal rabbit anti-murine TNFα IgG to *Plasmodium berghei* infected mice Grau *et al.* describe full protection against cerebral malaria. The focal accumulations of macrophages containing erythrocytes, which were observed in the brains of control animals, were not seen in the brains of mice immunized with anti-TNFα antibodies.

In summary, the teachings of Piguet (1987 and 1989) and Grau do not teach the use of the claimed antibodies to TNFα for the

treatment of these diseases.

Improper Combination of References

The Examiner believes that, in light of the known limitations of murine monoclonal antibodies for human therapy, together with the expected advantages of chimeric antibodies, one of ordinary skill in the art would have been motivated to combine Morrison's, Rathjen's and Möller's teachings to produce chimeric antibodies which bind to an epitope of human TNFα, antibodies which neutralize TNF biological activity and antibodies according to the teachings of Möller or Rathjen et al. and to select for those having the same functional properties as the M195 monoclonal antibody or the antibodies taught by Rathjen et al. Further, according to the Examiner, the claimed antibodies do not appear to differ in any unexpected or unobvious manner from those that one of ordinary skill in the art would have expected to obtain in view of the teaching of Möller in combination with Morrison.

Applicants disagree. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). A prima facie case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of certainty of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. Id.

As discussed above, related application Serial No. 08/324,799 and U.S. Patent No. 5,656,272 were allowed and issued, respectively, over essentially the Examiner's same combination of references (or references cumulative to these references). In

appreciation of the Examiner's time and in the interest of brevity, the full text of those arguments has not been repeated. The following is added with respect to the "new" arguments presented by the Examiner and to emphasize earlier arguments.

In particular, the Examiner states that "Morrison teaches that chimeric antibodies were considered to be superior to rodent antibodies for use in in vivo therapies." It is pointed out that the Examiner does not provide the specific portion of the reference in support of this contention. Respectfully, this is a mischaracterization of the teachings of Morrison. Morrison states that the production of chimeric antibodies "may" help to solve the problem of HAMA responses upon human administration of non-human antibodies. See, for example, the last column, first full paragraph of the Science article. These articles do not provide any scientific data which might support this statement. In fact, it is clear from the clinical results provided in the specification and literature of record that chimeric antibodies also generate a "HAMA" response. Thus, it is clear that the Examiner's conclusion that the person of ordinary skill in the art would be motivated to chimerize a murine antibody "to prevent human anti-murine antibody antibodies (HAMA)" is erroneous. It is noted that this position is partially retracted on page 14 of the action.

The Examiner states in the reasons for the rejection that TNF is "small and would be expected to possess a rather limited number of epitopes." Support for the assertion is not seen in this record. Also, the relevance of the assertion is also not seen. To the extent that it relates to the issue of rejected Claims 110-112, 115-118 and 124 (which provide limitations relating to the epitopic specificity), it is clear that a number of antibodies are known in the art with distinct specificities and distinct properties. This is evidenced by Rathjen. There is no motivation provided by the Examiner to select antibodies which bind to the epitopes defined in each of these claims (from the

numerous anti-TNF antibodies that can possibly be manufactured), much less the specific A2 antibody for chimerization.

Objective Evidence of Nonobviousness

As consistently recognized by the courts, the determination of nonobviousness must include, as relevant evidence, the "secondary considerations" of Graham v. John Deere, 383 U.S. at 17; 148 U.S.P.Q. at 467.

The secondary considerations described in Graham have been accorded significant weight by the Federal Circuit, as described in Glaros v. H.H. Robertson Co.: "The Federal Circuit has... repeatedly emphasized the importance of the inquiry into secondary considerations, such as the commercial success of the invention and the prior failure of others, as the strongest precaution against judging an invention from the perspective of 20/20 hindsight." 224 U.S.P.Q. 1037, 1038 (N.D. Ill. 1984), aff'd 230 U.S.P.Q. 393 (Fed. Cir. 1986). Further, in Stratoflex, Inc. v. Aeroquip Corp., the Federal Circuit stated:

> [E]vidence rising out of the so-called "secondary considerations" must always when present be considered en route to a determination of obviousness... Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.

218 U.S.P.Q. 871, 879 (Fed. Cir. 1983).

The secondary considerations set forth in Graham include, but are not limited to, unexpected results of the invention in relation to the prior art, expressions of disbelief by experts, and evidence that the invention has satisfied a long-felt need in the relevant field. The evidence regarding Applicants' invention clearly establishes all of these factors.

As indicated in Exhibits 1-3 and incorporated herein in their entirety, researchers have performed clinical studies which

demonstrate the safety and efficacy of administering the chimeric anti-TNF antibody cA2 to treat a TNF-mediated disease, rheumatoid arthritis (RA). The patients selected for the clinical studies had long-term, severe refractory disease and a history of failed therapy with several standard disease modifying anti-rheumatic drugs (DMARDs). Thus, the experiences of these patients clearly show long-felt and unsolved need for treatment for this potentially devastating disease. The fact that others in the field had tried for years to achieve a result, yet had failed, "is virtually irrefutable evidence that the [invention] would not have been obvious to those skilled in the art when it was invented." Panduit Corp. v. Dennison Mfg. Co., 227 U.S.P.Q. 337, 248-349 (Fed. Cir. 1985). Nonetheless, despite the duration and severity of their illnesses, the patients treated with chimeric anti-TNF antibody (cA2) experienced significant improvements and tolerated the treatments well, even upon multiple administration. (See e.g., Elliot *et al.* 1993, supra, at 1685-1688; Elliott *et al.* 1995, supra, at 142-144; Maini *et al.* 1995, supra, at 206-211 (Exhibits 1-3)). These unexpected results in relation to the prior art are objective evidence of nonobviousness as set forth in Graham.

Furthermore, the magnitude of these results in the treatment of a TNFα-mediated disease could not have been reasonably predicted from the prior art references. As noted in Exhibit 1 on page 1688, due to multiple and overlapping effects of cytokines such as IL-1 and TNFα and the fact that cytokines induce production of other cytokines and of themselves, there had been pessimism about whether targeting a single cytokine in vivo would have any beneficial effect. See, e.g., Exhibit 4 at page 177 ("...the most important question regarding cytokine intervention in rheumatic disease lies not in its technical feasibility but in the likely effect of interfering with only one cytokine within what is undoubtedly a very complex network. It seems highly improbable that a single cytokine holds the key to

RA synovitis."); Exhibit 5 at page 370 ("...the relevance of tumor necrosis factor and the biological outcome of its banishment by a monospecific inhibitor remain in doubt..."); Exhibit 5 at page 371 ("Unidimensional attacks on aberrant immune pathways might have limited effect on the underlying disease process"). Initial skepticism as to the merits of an invention by experts in the field supports the nonobviousness of this invention. Hughes Tool Co. v. Dresser Industries, Inc., 2 U.S.P.Q.2d 1396, 1402 (Fed. Cir. 1987). The Examiner states that "even if other cytokines were involved, a substantial activity of the pro-inflammatory cytokines IL-1 and TNFαare both reduced with anti-TNFα antibodies" citing the teachings of Elliot *et al.* 1995 and Maini *et al.* 1995. Applicants respectfully disagree that the teachings of 1995 references can serve as standards for obviousness of this application which was filed in 1991.

Since the claimed invention has led to unexpected results, and clearly satisfies a long felt but unsatisfied need, the secondary considerations, as set forth in Graham, preclude a finding of obviousness. Furthermore, the prior art references do not describe or suggest Applicants methods of treating TNFα-mediated disease in humans by administering chimeric anti-TNF antibodies, do not provide a reasonable expectation of achieving such antibodies having reduced immunogenicity and a therapeutic benefit, and do not reasonably suggest that the unexpected and superior results achieved and described herein were possible. Moreover, given the allowance (Serial No. 08/324,799) and issuing (U.S. Patent No. 5,656,272) of two related applications which contain claims similar to those in the present application, it is apparent that the rejections based on § 103 have been overcome.

The Examiner's Response to Applicants' Remarks

The Examiner stated in this Office action that the Remarks were not convincing. Specifically, the Examiner states that Applicants' argued "That the references themselves do not suggest

the combination of the A2 epitope or any particular isotype." It is agreed that this is a part of the argument of record relating to the non-obvious selection of the epitope and/or the isotype relating to specific claims of record. Please note that each claim must be considered separately. Regarding the Examiner's observation that there exists a possibility that the A2 epitope is the same or similar to the M195 epitope, the Examiner does not address Applicants' argument. Even if the epitope is the same, there is nothing in the prior art which would teach that it would be desirable to select antibodies which bind that specific epitope (from the many possible antibodies that can be generated) for chimerization. The Examiner's assertion that "routine" anti-TNF antibodies may also bind the A2 epitope is not understood. The fact that it is possible to raise antibodies which possess the same or similar epitopic specificity as the A2 antibody establishes that the claims are enabled for the full scope. It does not follow that it would therefore be obvious to select from all possible anti-TNF antibodies those antibodies which possess the claimed epitopic specificities for chimerization.

Regarding the selection of the isotype (relating specifically to rejected Claims 113-118), the fact that different isotypes were known to possess different properties does not suggest that the selection of a specific isotype for the purposes of manufacturing an anti-TNF antibody for therapeutic purposes was obvious. There is nothing of record which might suggest that, in treating TNF-mediated diseases with an anti-TNF antibody, that the IgG1 isotype is desirable or advantageous. Applicants have provided evidence that the isotypes are not "equivalent", "mere alternatives" or "interchangeable", as the Examiner has characterized them. See Scallon *et al.*, *Cytokine*, *7(3)*:251-259 (1995), discussed in more detail in the last Response. The Examiner inappropriately employs hindsight in dismissing this evidence, stating that "One of ordinary skill in the art would have conducted a simple screening procedure or

referred to the general wealth of knowledge in the art at the time the invention was made to select an isotype with the desired activities." Firstly, the Examiner has not provided a single reference at the time the invention was made which might suggest that one isotype would be advantageous over other isotypes for treating anti-TNF mediated diseases. Thus, the latter portion of the Examiner's position is completely unsupported. Regarding the former portion of the Examiner's statement, the assertion that a screening could have been performed (or referring to the Examiner's earlier reference to the fact that methods for producing chimeric antibodies were known), does not support the conclusion that the result achieved by the claimed antibodies possessing an IgG1 isotype was expected. Please note that 35 U.S.C. 103 states that "Patentability shall not be negatived by the manner in which the invention was made."

The Examiner then refers to Applicants' arguments relating to the fact that the references relied upon by the Examiner provide only in vitro and animal data. The Examiner apparently does not disagree with any of the technical observations made relating to each reference or the combination. He does rely upon subsequently published results and observations.

Elliot *et al.* (1995) and Maini *et al.* (1995)

Specifically the Examiner states that in regards to Brennan *et al.* (1989), Elliot *et al.* (1995) and Maini *et al.* (1995) teach that *in vivo* therapeutic intervention in the treatment of rheumatoid arthritis using anti-TNFα antibodies was based on the *in vitro* teachings of Brennan *et al.* (1989). It is unfair to evaluate obviousness based upon the teachings of references published in 1995 which consider not just the teachings of Brennan but also the results of successful clinical trials. A skilled artisan, on the basis of the information disclosed at the time of the filing of the application in 1991, would not have been motivated to conclude that the *in vitro* teachings of Brennan

et al. (1989) would be obvious for *in vivo* treatments, as Elliot and Maini did in 1995.

The Examiner states that the "purpose of *in vitro* and animal experimentation is to provide one of ordinary skill in the art with a correlation or reasonable expectation of what would occur in a human." Applicants do not disagree that such a correlation is desirable and is accurate in many instances. However, as the Examiner acknowledged, not all animal models correlate well. In fact, the Examiner, earlier in the prosecution of this application, asserted that animal models for treating septic shock cannot be extrapolated at all. See page 3 of the action mailed September 18, 1996. Applicants have provided technical basis in support of the argument and have, thus, rebutted the Examiner's rejection.

Applicants argued that the prior art suggested that the inhibition of a single cytokine would not necessarily be sufficient to alleviate the disease. In response, the Examiner reminds Applicants that "the claims are drawn to a method of treatment not a cure." It is apparently the Examiner's position that even if the prior art taught that other cytokines are involved, a "substantial effect would have been expected." There is no evidence of record which would support the Examiner's conclusion that the clinical effect achieved by TNF blockade would be "expected" to be "substantial", except for the subsequent clinical results achieved from the cA2 antibody of the present claims. Again, the Examiner's position is unsupported by the record. More specifically to the Examiner's point, it is agreed that the claims are not drawn to a disease cure, but to a treatment of disease. Thus, even if some therapeutic benefit was expected from the prior art, the actual results achieved and reported herein was totally unexpected. Thus any prima facie case of obvious which may have resulted has been rebutted.

The Examiner refers to a decade of routine administrations of antibodies to humans as of the time the invention was made.

Applicants specifically take issue with the unsupported assertion. It is impossible, based upon such a vague assertion, for Applicants to place the human therapies as envisioned by this Examiner in their proper context. In any event, the fact is irrelevant to the issue. Therapies for treating TNF-mediated diseases in humans by the administration of anti-TNF antibodies were not known. Thus, the fact that other antibodies in the treatment of other disease states were successful is not relevant to the issue of whether the person of ordinary skill in the art would reasonably expect the administration of a chimeric anti-TNF antibody (much less the specific anti-TNF antibodies described in the present claims) to possess the therapeutic benefits described herein.

The Examiner points to the contents of the earliest claimed priority date, it is believed that the Examiner is attempting to state that the clinical results added in the later filed continuation-in-part applications cannot be relied upon to rebut the rejection. Of course, this is incorrect. See, for example, In re Davies, 177 USPQ 381 (CCPA 1973) which illustrates the point.

The Examiner states that "determining the pharmacokinetics of an antibody was routine" and "demonstration of specific binding and ability to neutralize is a good indication of the affects in vivo." Even if this is true, it does not support the conclusion that the clinical result of the antibody would be as achieved and reported herein. Thus, the issue of whether the antibody will bind TNF *in vivo* is distinct from the issue of whether that binding and any subsequent neutralization will be clinically beneficial (or how much of a clinical benefit can be expected).

The Examiner dismisses the teachings of "Kingsley *et al.* and Feldman", relied upon to establish that persons in the art were skeptical about ability to treat diseases by TNF blockade. His reason appears to be in the fact that the Brennan and Shalaby articles are not cited therein. It is not clear precisely what

the Examiner is referring to. In any event, Dr. Feldmann was a coauthor of the 1989 Brennan article. Thus, it is unlikely that any subsequent articles by Dr. Feldmann were drafted "unaware" of his own earlier publication. In any event, the Examiner's observation that a journal article is not cited in a review article does not support the conclusion that the article (or an article substantially cumulative to or more relevant than the article relied upon in the rejection) was not known to the author or that the opinion of the author would have been modified by those results. The caselaw clearly establishes that such teachings must be considered by the Examiner in evaluating obviousness.

In summary, the references relied upon in the rejection do not teach chimerizing an anti-TNF antibody, do not teach that the selection of particular epitopes and/or isotypes, and do not teach (with a reasonable expectation of success) that such antibodies would be clinically beneficial in treating TNF-mediated disease. Even if arguendo, it would have been obvious to manufacture a chimeric antibody (e.g., with the claimed epitopic specificities and/or isotype) and administer that antibody in the treatment of the disease states discussed in the rejection (e.g., shock resulting from GVHD), the references do not teach that the clinical results actually achieved would be expected. Withdrawal of the rejection is requested.

Objection of Claims 119-122

The Examiner states that Claims 119-122 would be allowable if written as independent claims. Claims 119 and 120 have been amended and are now independent claims. Claims 121 and 122 depend now on the method and recited diseases in amended Claims 119 and 120. Thus, withdrawal of the objection of Claims 119-122 is respectfully requested.

Request for Interview

Applicants hereby request an interview with the Examiner before issuance of the next Office Action.

CONCLUSION

It is respectfully submitted that the claims are now in condition for allowance. If the Examiner feels that a telephone conference would be helpful in expediting the prosecution of the application, the Examiner is encouraged to telephone the undersigned at (617) 861-6240.

Respectfully submitted,

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